07-10-06

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Docket No.: NY-LUD 5466-US7-DIV (10112540)
(PATENT)

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Air bill No. EV 793662564 US, in an envelope addressed to: MS Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: July 7, 2006 Signature: Fani Malikouzakis
(Fani Malikouzakis)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Elisabeth Stockert et al.

Application No.: 10/023,182 Confirmation No.: 3379

Filed: December 17, 2001 Art Unit: 1642

For: ISOLATED NUCLEIC ACID MOLECULES ENCODING ESO-1 PEPTIDES AND USES THEREOF Examiner: M. T. B. Davis

AMENDMENT TO THE BRIEF ON APPEAL

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is submitted pursuant to the telephone discussion with the Examiner. Please amend the Brief on Appeal as follows.

Page 1, change "Breif" to -- BRIEF --.

IN THE CLAIMS

34. (Currently Amended) The isolated protein of claim ~~33~~ 32, wherein said MHC molecule is a Class II molecule.

35. (Currently Amended) The isolated protein of claim ~~33~~ 32, wherein said MHC molecule is a Class I molecule.

REMARKS

In addition to the corrections made supra, attached hereto is a replacement brief with the Examiner's suggested corrections.

A substantive response is urgently requested.

Respectfully submitted,

By _____

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Docket No.: NY-LUD 5466-US7-DIV (10112540)
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For: ISOLATED NUCLEIC ACID MOLECULES ENCODING ESO-1 PEPTIDES AND USES THEREOF Examiner: M. T. B. Davis

BRIEF ON APPEAL
(37 C.F.R. § 41.37)

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. § 41.37(a)(1), appellants are submitting this Brief on Appeal within 1 month of the decision following their Pre-Appeal Request for Review, which is dated November 23, 2005. This decision provides the option of filing the Brief within two months of the Notice of Appeal (October 12, 2005), or one month from the decision (November 23, 2005), which is longer.

Pursuant to 37 C.F.R. § 41.37(a)(2), the fee set forth in 37 C.F.R. § 41.20(b)(2) is included herewith.

As is required by 37 C.F.R. § 41.37(c)(1), the following is provided.

I. REAL PARTY IN INTEREST

The real parties in interest for this appeal are the assignees, Ludwig Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center, The Cornell Research Foundation, Inc., and Academisch Ziekenhuis Leiden.

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

To the best of the knowledge of the appellants, the assignees, and the undersigned legal representative, there are no prior or pending appeals, interferences, or judicial proceedings which may be directly related to, directly affect, or be directly affected by or have a bearing on the Board's decision in this, pending appeal.

III. STATUS OF CLAIMS

At present claims 32, 34-37, 40 and 41 are pending.

Claims 32, 34-37 and 40 have been rejected. The rejection of these claims is appealed herein.

Claim 41 has been objected to, and is not appealed.

This application is a divisional of a prior application, filed with claims 1-21. All were canceled by Preliminary Amendment, and claims 22-31 were added, also via Preliminary Amendment. Via a second Preliminary Amendment, claims 32-39 were added.

Following restriction, claims 32-37 were elected, and claims 22-31 were canceled. Claims 40 and 41 were added. Hence, claims 32-41 were before the Examiner for examination. In the course of prosecution, claims 33, 38 and 39 were canceled.

IV. STATUS OF AMENDMENTS

A final rejection issued on June 3, 2005. Following a personal interview on June 21, 2005, an amendment after final rejection was filed on August 3, 2005. The Advisory Action of October 6, 2005, does not indicate if the Amendment was entered; however, as rejections were withdrawn, it appears that it was.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter as represented by independent claim 32, is an isolated protein, which is a portion of the protein, known as NY-ESO-1. NY-ESO-1 is described in U.S. Patent No. 5,804,381, which is a precursor to the claimed protein.

NY-ESO-1 is a highly immunoreactive protein, which is processed by cells, intracellularly, to generate peptides which bind to MHC molecules.

Page 5, lines 12-14 describe the isolation technique for obtaining NY-ESO-1. Examples 1-4 elaborate on its identification as a cancer marker.

Page 14 of the specification describes how anti-NY-ESO-1 antibodies were found in cancer patients, clearly indicating that the protein generated an immune response.

Example 7 describes proteins that consist of some but not all of the amino acid sequence of NY-ESO-1. In particular, please note lines 20-26 of page 18, and also page 19, lines 4-5.

The fact that the proteins do provoke CTL responses is shown at page 19, line 16 - the end of example 7.

Example 9 discusses how all of the variant forms of the protein reacted with antibodies equally. Additional experiments, set forth at examples 10 and 11, show the proliferation of CTLs, with the use of the proteins. Specific proteins are described as "the best stimulators of CTLs" at page 25, indicating that others also stimulated CTLs. Example 13 describes how to identify candidate peptides, based upon NY-ESO-1 as MHC binders. With reference to variants that consist of amino acids 10-180 and 10-121, all of these peptides are encompassed by the variant 10-180, and 22 by the variant 10-121.

SEQ ID NOS: 4, 5, and 6 are:

SLLMWITQCFL;
SLLMWITQC, and
QLSLLMWIT

These correspond to amino acids 157-167, 157-165, and 155-163, as can be determined by review of either .the full sequence of NY-ESO-1, or via review of the second and third antepenultimate peptides at page 26, which present sufficient information to splice amino acids 154-167 together.

In their amendment of April 1, 2005, appellants provided a list of peptides which had been shown to expressly stimulate CTLs, and which bound to either MHC-Class I or Class II molecules. Note the similarity between, e.g., the peptide of page 26, consisting of amino acids 79-88, and that consisting of amino acids 80-88, that at page 26 consists of amino acids 96-104, and that of 94-102 and that at page 26 consisting of amino acids 162-170, and that in the evidentiary document consisting of amino acids 157-170.

VI. GROUNDS OF OBJECTION TO BE REVIEWED ON APPEAL

There is a single ground of rejection presented. Claims 32, 34-37 and 40 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to satisfy the Written Description requirement.[1]

Appellants contend that this rejection is erroneous and seek reversal thereof.

VII. ARGUMENT

It is believed that it is worthwhile to repeat claim 32 the single independent claim here, to clarify any confusion as to the nature of the rejection:

An isolated protein consisting of an immunoreactive portion of a protein encoded by an isolated nucleic acid molecule consisting of the nucleotide sequence of SEQ ID NO: 1, wherein said immunoreactive portion of a protein is processed by a cell to form a peptide which complexes to an MHC molecule and provides a T cell response.

To explain the claim, SEQ ID NO: 1 encodes a full length protein. The full length protein is not claimed. Rather, molecules that constitute a portion of this molecule are claimed.

These portions of the molecule have to be large enough so that, when taken up by cells, they are processed to peptides that are presented by MHC molecules.

The Examiner does not appear to have issues with the "portion" language in the claim, nor does the Examiner take issue with the question of whether or not the portions of the protein can be processed. Rather, to the extent Appellants have been able to follow the rejection, it seems to be that an insufficient number of reactive peptides are disclosed. Please note, e.g., page 3 of the final rejection of June 3, 2005:

> "Although SEQ ID NO: 4, 5, 6, are found to bind to HLA-A2 and provoking T cell proliferation, and although several peptides from SEQ ID NO: 1 that have HLA binding motifs are disclosed in the specification, there is no common structure among these peptides, and there is no disclosed common structure that is correlated with the ability to complex with an MHC molecule and elicit a T cell response."

With all due respect, however, this is incorrect.

First, the peptides that are disclosed - and there are more than several - DO share a disclosed, common structure. They must consist of an amino acid sequence found in SEQ ID NO: 1, and they must be of the proper size to bind to MHC molecules.

The positions of the disclosed peptides within SEQ ID NO: 1 are provided in the list of over 20 peptides at page 26.

With respect to a common structure "correlated with the ability to complex with an MHC molecule and elicit a T cell response," several points must be made. First, the structure needed to bind to a particular MHC molecule does vary depending on the MHC molecule; however, appellants disclose this rule. Attention is drawn, as it has been before, to page 25, Parker et al., *J. Immunol.*, 142: 163 (1994), which was incorporated by reference, as well as the papers by D'Amaro and Drijfhout, cited at page 24 and incorporated by reference.

A specification need not teach, and preferably leaves out, that which is known to the art. Hybritech, Inc. v. Monoclonal Antibodies.

Appellants incorporated these papers by reference so that there would be no need to present lists of so-called "binding motifs." All one need do is to look up a motif for, e.g., HLA-B8, in these references, and she would find out (i) the size of peptides, which bind to

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[1] A prior lack of enablement rejection has been withdrawn.

HLA-B8, and (ii) what amino acids are required, and at what positions. That is what appellants did to generate the referred to Table.

Appellants do not, and never have, disagreed with the principle that binding to an MHC molecules does not guarantee provocation of a T cell response; however, the examples teach very clearly how to determine if a T cell response is generated. These are standard assays, certainly not proprietary to appellants, and certainly well within the skill of the artisan.

Thus to summarize what Appellants teach, with relation to what is claimed:

(i) There is a reference, full length protein described in the specification;

(ii) What is claimed are portions of (i), which are processed by cells to MHC presented peptides, where the complex of MHC and peptide generates a T cell;

(iii) The rules for binding to different MHC molecules are known and are incorporated by reference;

(iv) Appellants applied the rules of (iii) to the claimed molecules, and provide a list of pertinent peptides;

(v) The methods for determining if peptides - function as T cell generators are known, and taught in the specification; and

(vi) Appellants describe three peptides which meld the structural and functional requirements of the claims.

Notwithstanding this, the Examiner brushes aside all evidence, misinterprets the claims and prosecution history, and attempts to apply a *per se* rule that one can claim specifically disclosed species, and nothing more.

The final rejection of June 3, 2005, refers back to the Office Action of January 3, 2005, as the basis for the rejection. That rejection states that the lack of a definition of "immunoreactive portion" and the large size of the NY-ESO-1 protein the claim encompasses "numerous different immunoreactive portions." Indeed, this is true; however, no case

precedent holds that the breadth of a claim de facto means it fails to satisfy the written description requirement.

The Examiner then goes into a discussion of B cell antigen receptors, which is puzzling.

ORIGINAL claim 32 was indeed broad enough to embrace both T cell and B cell responses. Originally, claim 32 did not specify the nature of the response, and dependent claim 33 did in fact recite a T cell response.

During a telephone interview, i.e., one which took place on December 14, 2004, the issue of support for a B cell response was discussed. In the amendment dated April 1, 2005, applicants amended the claim to require a T cell response and stated, at page 4:

> "The claims thus require the protein recited therein to be converted to a molecule which, when complexed to an MHC molecule, generates a T cell response."

Thus, discussions of B cell epitopes are completely out of order. The discussion of T cell epitopes which the Examiner provides is an accurate recitation of what is known of T cell molecular biology; however, it is submitted that it is not pertinent to what is claimed.

The Examiner cites to the case of University of California v. Eli Lilly, 43 USPQ2d 1398 (Fed. Cir. 1997), as allegedly supporting her position; however, Eli Lilly *per se* does not support the Examiner's position. Further, developments in the law since Eli Lilly, as well as the Interim Written Description Guidelines clearly show that the Examiner's position is not correct.

Appellants drew the Examiner's attention to Example 14 of those Guidelines. To recapitulate, that example describes a situation where one protein was disclosed. No examples of variants were shown. An assay was described, showing how to test variants.

The claim was to proteins "at least 95% identical" to the reference, which catalyze a reaction in the way the disclosed species does. According to the Guidelines:

> "The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity."

According to the example, the disclosure meets the Written Description requirement.

Appellants submit that their specification satisfies everything set forth in the Example. Every claimed molecule must have a sequence found in the protein encoded by SEQ ID NO: 1. No variations are possible. Processes for truncating full length proteins, are well known. Appellants disclose what amino acids, and what "spacing" in between these is necessary for binding to particular MHC molecules. They teach assays for determining if the protein is in fact processed to a peptide which stimulates T cells.

Yet, according to the Examiner, Example 14 is irrelevant because "only 3 peptides" are taught which satisfy the claim, and the claim is generic.

Appellants question how this analysis shows that Example 14 is not applicable. The claim is Example 14 was generic. No structural information relating to active sites is disclosed. Only a single embodiment is shown. Why then should this case be treated differently than is provided in the Guidelines?

Enzo Biochem., Inc., v. Gen-Probe, Inc., 63 USPQ2d 1609 (Fed. Cir. 2002), and The Eli Lilly case, *supra*, establish quite clearly that what the Examiner appears to require, i.e., complete structures of an unspecified quantity of peptides with examples showing that they actually provoke T cells, is not required. Indeed, according to Enzo Biochem:

> "The written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed relevant, identifying characteristics..., i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics."

Enzo at 1613. The present claims require a specific function, i.e., the ability to be processed to a T cell epitope. There is no evidence put forth by the Examiner that one of ordinary skill in the art would be unable to determine if a claimed molecule possessed these characteristics. (Note that this is NOT the same as showing few or no molecules do, which would be an enablement issue. Lack of enablement is not an issue here, and in any event, there is no evidence of that either.)

Structurally, the claims require a starting point, i.e., the amino acid sequence encoded by SEQ ID NO: 1, coupled with the function discussed *supra*. Structure is correlated with function, as appellants have pointed out, many times, by reference to what has been incorporated by reference. They describe three species which function. They teach how to determine what does and does not function.

Nothing advanced by the Examiner refutes any of this. As such, a *prima facie* case has not been made out, and the rejection cannot be deemed proper.

VIII. CLAIMS

A copy of the clean claims involved in the present appeal is attached hereto as Appendix A.

IX. EVIDENCE

No evidence pursuant to §§ 1.130, 1.131, or 1.132 or entered by or relied upon by the Examiner is being submitted.

X. RELATED PROCEEDINGS

No related proceedings are referenced in II. Above or copies of decisions in related proceedings are not provided hence no Appendix is included.

XI. CONCLUSION

For all of the reasons advanced, *supra* it is respectfully submitted that the rejection of claims 32, 34-37 and 40 under 35 U.S.C. § 112, first paragraphs lacking adequate written description is improper, and should be reversed.

Respectfully submitted,

By _____

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CLAIMS APPENDIX A
(37 C.F.R. § 41.37(C)(VIII)

Listing of Claims on Appeal

32. An isolated protein consisting of an immunoreactive portion of a protein encoded by an isolated nucleic acid molecule, consisting of the nucleotide sequence of SEQ ID NO: 1, wherein said immunoreactive portion of a protein is processed by a cell to form a peptide which complexes to an MHC molecule and provides a T cell response.

34. The isolated protein of claim 32, wherein said MHC molecule is a Class II molecule.

35. The isolated protein of claim 32, wherein said MHC molecule is a Class I molecule.

36. A composition comprising the isolated protein of claim 32, and an adjuvant.

37. The composition of claim 36, wherein said adjuvant is a saponin, GM-CSF, or an interleukin.

40. The isolated protein of claim 32, wherein said immunoreactive portion of the protein is an amino acid sequence of a tumor rejection antigen.

41. The isolated protein of claim 40, wherein said amino acid sequence is the amino acid sequence set forth in SEQ ID NO: 4, 5, or 6.

EVIDENTIARY APPENDIX
(37 C.F.R. § 41.37(C)(IX)

None.